WHAT IS CLAIMED IS:

1. A method comprising:

(1) providing a set of models, wherein each model comprises three-dimensional structural information for a ligand or a ligand:macromolecule complex;

wherein each model is related to the other models of the set by a homologous structural feature;

(2) mapping spatial relationships between the models such that the models are superimposed with respect to the homologous structural feature;

(3) identifying one or more pairs of matching bonds between ligands of the set, wherein the matching bonds comprise a bond of a first ligand (B1) and a bond of a second ligand (B2) that are superimposed in step (2) such that

(i) an atom at each end of the bond (B1) is within 1.8 angstrom of an atom at each end of the bond (B2),

(ii) the bond (B1) and the corresponding bond (B2) are of the same bond order, and

(iii) the bond (B1) and the corresponding bond (B2) are related by an angle of 30° or less;

(4) selecting a plurality of subsets of atoms and/or bonds from each ligand;

wherein each subset comprises a bond and/or, an atom connected to the matching bond;

(5) generating output ligands, each output ligand comprising atoms and/or bonds of a first subset and atoms and/or bonds of a second subset, wherein the first subset and the second subset comprise atoms and/or bonds derived from opposite ends of the matching bond.

2. The method of claim 1, wherein the output ligands comprise all atoms represented in the ligands of step (1).

3. The method of claim 1, wherein each model of the set comprises a ligand:macromolecule complex.

4. The method of claim 1, wherein one or more models of the set consist of a ligand.

5. The method of claim 3, wherein the macromolecule is a protein or a nucleic acid.

6. The method of claim 5, wherein the macromolecule is a protein kinase, a G-protein coupled receptor, an immunoglobulin superfamily protein, a protease, or a zinc-finger containing protein.

7. The method of claim 3, wherein each model of the set comprises an identical macromolecule.

8. The method of claim 1, wherein the structural information is derived from a physical observation.

9. The method of claim 3, wherein the structural information comprises information derived by a computational inference.

10. The method of claim 1, wherein the ligand is a small molecule.

11. The method of claim 1, wherein the ligands are less than 1000 atomic mass units (a.m.u.).

12. The method of claim 1, wherein the ligands are less than 600 a.m.u.

13. The method of claim 1, wherein the homologous feature comprises structural homology between the ligands.

14. The method of claim 13, wherein the structural homology comprises homology between a framework of the ligands.

15. The method of claim 13, wherein the structural homology comprises homology between a pharmacophore model of the ligands.

16. The method of claim 5, wherein the macromolecule is a protein, and wherein the homologous feature comprises structural homology between the proteins.

17. The method of claim 16, wherein the homology comprises at least 25% amino acid homology.

18. The method of claim 17, wherein the homology comprises at least 40% amino acid homology.

19. The method of claim 17, wherein the homology comprises a shared polypeptide fold.

20. The method of claim 1, wherein the set comprises at least three models.

21. The method of claim 1, wherein the method further comprises selecting the set of models from a plurality of models prior to the providing of step (1).

22. The method of claim 21, wherein the selecting comprises identifying models comprising a homologous structural feature.

23. The method of claim 22, wherein each model of the set comprises a ligand:macromolecule complex, and wherein the homologous structural feature comprises desired degree of structural homology between the macromolecules.

24. The method of claim 1, further comprising the steps of:

(6) comparing output ligands of step (5) to the ligands of step (1); and

(7) storing output ligands that are not identical to the ligands used in a previous iteration of steps (2)-(5) in a machine-readable medium.

25. The method of claim 24, further comprising generating one or more output models, wherein each output model comprises the stored ligand docked into a target macromolecule.

26. The method of claim 25, further comprising refining the output models.

27. The method of claim 26, wherein the refining comprises performing energy minimization computations.

28. The method of claim 27, further comprising evaluating the output models.

29. The method of claim 28, further comprising assigning a score to each output model based on the evaluating.

30. The method of claim 29, further comprising obtaining a composition comprising a compound corresponding to a ligand from a subset of output models, wherein the subset comprises output models having a score in a preselected range.

31. The method of claim 30, further comprising evaluating the composition.

32. The method of claim 31, wherein the evaluating comprises determining the ability of the compound to bind a target macromolecule, or the ability of the compound to modulate activity of a target macromolecule.

33. The method of claim 24, wherein steps 2-7 are repeated, and wherein the models superimposed in step (2) comprise the stored output ligands of step (7).

34. The method of claim 33, wherein the repeating is automatic.

35. The method of claim 34, wherein the repeating stops when each ligand of step (7) is identical to a ligand provided in the previous step (2) of the repetition.

36. The method of claim 1, wherein the structural information comprises hydrogen atoms of the ligands and the bonds to hydrogen atoms.

37. The method of claim 1, wherein the structural information does not comprise hydrogen atoms of the ligands.

38. The method of claim 1, wherein the ligands comprise a macrocyclic moiety, and wherein at least two matching bonds are identified within the macrocycle of each ligand.

39. A method comprising:

(1) selecting a set of models from a plurality of models, wherein the selecting comprises identifying models comprising a homologous structural feature, wherein each model comprises three-dimensional structural information for a ligand:macromolecule complex;

(2) providing the set of models;

(3) mapping spatial relationships between the models such that the models are superimposed with respect to the homologous structural feature;

(4) identifying one or more pairs of matching bonds between ligands of the set, wherein the matching bonds comprise a bond of a first ligand (B1) and a bond of a second ligand (B2) that are superimposed in step (2) such that

(i) an atom at each end of the bond (B1) is within 1.8 angstrom of an atom at each end of the bond (B2),

(ii) the bond (B1) and the corresponding bond (B2) are of the same bond order, and

(iii) the bond (B1) and the corresponding bond (B2) are related by an angle of 30° or less;

(5) selecting a plurality of subsets of atoms and/or bonds from each ligand;

wherein each subset comprises a bond and/or, an atom connected to the matching bond;

(6) generating output ligands, each output ligand comprising atoms and/or bonds of a first subset and atoms and/or bonds of a second subset, wherein the first subset and the second subset comprise atoms and/or bonds derived from opposite ends of the matching bond.

40. A database of output ligands, the database comprising a plurality of records, each record comprising information representing the arrangement of atoms in the output ligands, wherein the output ligands are generated by the following steps:

(1) providing a set of models, wherein each model comprises three-dimensional structural information for a ligand or a ligand:macromolecule complex;

wherein each model is related to the other models of the set by a homologous structural feature;

(2) mapping spatial relationships between the models such that the models are superimposed with respect to the homologous structural feature;

(3) identifying one or more pairs of matching bonds between ligands of the set, wherein the matching bonds comprise a bond of a first ligand (B1) and a bond of a second ligand (B2) that are superimposed in step (2) such that

(i) an atom at each end of the bond (B1) is within 1.8 angstrom of an atom at each end of the bond (B2),

(ii) the bond (B1) and the corresponding bond (B2) are of the same bond order, and

(iii) the bond (B1) and the corresponding bond (B2) are related by an angle of 30° or less;

(4) selecting a plurality of subsets of atoms and/or bonds from each ligand;

wherein each subset comprises a bond and/or, an atom connected to the matching bond;

(5) generating output ligands, each output ligand comprising atoms and/or bonds of a first subset and atoms and/or bonds of a second subset, wherein the first subset

and the second subset comprise atoms and/or bonds derived from opposite ends of the matching bond;

(6) comparing output ligands to the ligands of step (1);

(7) storing output ligands that are not identical to the ligands of step (1) in a machine-readable medium;

(8) repeating steps (2)-(7), wherein the models superimposed in step (2) comprise the stored output ligands of step (7); wherein the repeating stops when each output ligand of step (7) is identical to a ligand provided in the previous step (2) of the repetition.

41. The database of claim 40, further comprising 3-D structural positions of atoms of the output ligands.

42. An apparatus comprising:

(a) a memory that stores executable instructions; and

(b) a processor that executes the instructions to:

(1) provide a set of models, wherein each model comprises three-dimensional structural information for a ligand or a ligand:macromolecule complex;

wherein each model is related to the other models of the set by a homologous structural feature;

(2) map spatial relationships between the models such that the models are superimposed with respect to the homologous structural feature;

(3) identify one or more pairs of matching bonds between ligands of the set, wherein the matching bonds comprise a bond of a first ligand (B1) and a bond of a second ligand (B2) that are superimposed in step (2) such that

(i) an atom at each end of the bond (B1) is within 1.8 angstrom of an atom at each end of the bond (B2),

(ii) the bond (B1) and the corresponding bond (B2) are of the same bond order, and

(iii) the bond (B1) and the corresponding bond (B2) are related by an angle of 30° or less;

(4) select a plurality of subsets of atoms and/or bonds from each ligand;

wherein each subset comprises a bond and/or, an atom connected to the matching bond;

(5) generate output ligands, each output ligand comprising atoms and/or bonds of a first subset and atoms and/or bonds of a second subset, wherein the first subset and the second subset comprise atoms and/or bonds derived from opposite ends of the matching bond;

(6) compare output ligands to the ligands of step (1);

(7) store output ligands that are not identical to the ligands of step (1);

(8) repeat steps (2)-(7), wherein the models superimposed in step (2) comprise the stored output ligands of step (7);

wherein the repeating stops when each output ligand of step (7) is identical to a ligand provided in the previous step (2) of the repetition.

43. An article comprising machine-readable media that stores executable instructions, the instructions causing a machine to:

(1) provide a set of models, wherein each model comprises three-dimensional structural information for a ligand or a ligand:macromolecule complex;

wherein each model is related to the other models of the set by a homologous structural feature;

(2) map spatial relationships between the models such that the models are superimposed with respect to the homologous structural feature;

(3) identify one or more pairs of matching bonds between ligands of the set, wherein the matching bonds comprise a bond of a first ligand (B1) and a bond of a second ligand (B2) that are superimposed in step (2) such that

(i) an atom at each end of the bond (B1) is within 1.8 angstrom of an atom at each end of the bond (B2),

(ii) the bond (B1) and the corresponding bond (B2) are of the same bond order, and

(iii) the bond (B1) and the corresponding bond (B2) are related by an angle of 30° or less;

(4) select a plurality of subsets of atoms and/or bonds from each ligand;

wherein each subset comprises a bond and/or, an atom connected to the matching bond;

(5) generate output ligands, each output ligand comprising atoms and/or bonds of a first subset and atoms and/or bonds of a second subset, wherein the first subset and the second subset comprise atoms and/or bonds derived from opposite ends of the matching bond;

(6) compare output ligands to the ligands of step (1);

(7) store output ligands that are not identical to the ligands of step (1);

(8) repeat steps (2)-(7), wherein the models superimposed in step (2) comprise the stored output ligands of step (7);

wherein the repeating stops when each output ligand of step (7) is identical to a ligand provided in the previous step (2) of the repetition.

44. An article comprising machine-readable media that stores executable instructions, the instructions causing a machine to:

(1) map spatial relationships between two or more models of ligands of a set such that the models are superimposed, wherein each model comprises three-dimensional structural information for a ligand;

(2) identify one or more pairs of matching bonds between ligands of the set, wherein the matching bonds comprise a bond of a first ligand (B1) and a bond of a second ligand (B2) that are superimposed in step (2) such that

(i) an atom at each end of the bond (B1) is within 1.8 angstrom of an atom at each end of the bond (B2),

(ii) the bond (B1) and the corresponding bond (B2) are of the same bond order, and

(iii) the bond (B1) and the corresponding bond (B2) are related by an angle of 30° or less;

(3) select a plurality of subsets of atoms and/or bonds from each ligand;

wherein each subset comprises a bond and/or, an atom connected to the matching bond;

(4) generate output ligands, each output ligand comprising atoms and/or bonds of a first subset and atoms and/or bonds of a second subset, wherein the first subset and the second subset comprise atoms and/or bonds derived from opposite ends of the matching bond.